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Iron Porphyrin-Catalyzed Three-Component Reaction of Ethyl Diazoacetate with Aliphatic Amines and β,γ-Unsaturated α-Keto Esters

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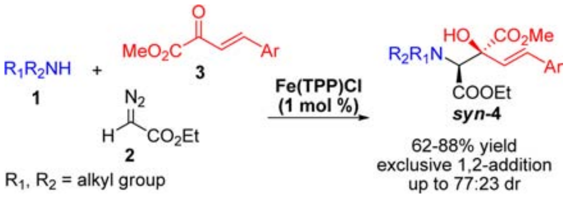
ABSTRACT



62-88% yield
exclusive 1,2-addition
up to 77:23 dr

An iron porphyrin-catalyzed three-component reaction of ethyl diazoacetate with aliphatic amines and β,γ-unsaturated α-keto esters is reported. The use of iron porphyrin catalyst allows aliphatic amines to be used as the substrate without encountering catalyst poisoning issue and a series of β-hydroxy-α-amino esters are produced in high yields with excellent regioselectivities.

Metal carbenoids generated from diazo compounds with transition-metal catalysts can undergo a variety of important synthetic transformations such as cyclopropanation, X−H (X = C, N, O, Si, S) insertion, and ylide formation.[1] In recent years, multicomponent reactions (MCRs) based on the trapping of ylide intermediates with different types of electrophiles have greatly enriched the arsenal of carbenoid chemistry and become a powerful tool for the synthesis of polyfunctional molecules.[2−4] In these types of MCRs, Rh(II) catalysts were most generally used for their high efficiency in decomposing diazo compounds into carbenoids. However, in certain types of MCRs, the rhodium catalyst was limited in its use to a narrow selection of substrates and undesired side reactions owing to catalyst poisoning and its excessive efficiency.[1a,5] For example, in the Rh(II)-catalyzed ammonium ylide trapping process, in order to avoid catalyst poisoning, only less basic aromatic

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[1] For leading reviews, see: (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1998. (b) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341. (c) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (d) Sun, X.-L.; Tang, Y. *Acc. Chem. Res.* **2008**, *41*, 937. (e) Zhang, Z.; Wang, J. *Tetrahedron* **2008**, *64*, 6577. (f) Zhu, S.-F.; Zhou, Q.-L. *Acc. Chem. Res.* **2012**, *45*, 1365. (g) Zhao, X.; Zhang, Y.; Wang, J. *Chem. Commun.* **2012**, *48*, 10162.

[2] For selected MCRs via the trapping of oxonium ylides, see: (a) Huang, H. X.; Guo, X.; Hu, W. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 1337. (b) Guo, X.; Huang, H. X.; Yang, L. P.; Hu, W. H. *Org. Lett.* **2007**, *9*, 4721. (c) Hu, W. H.; Xu, X. F.; Zhou, J.; Liu, W. J.; Huang, H. X.; Hu, J.; Yang, L. P.; Gong, L. Z. *J. Am. Chem. Soc.* **2008**, *130*, 7782. (d) Zhang, X.; Huang, H.; Guo, X.; Guan, X.; Yang, L.; Hu, W. *Angew. Chem., Int. Ed.* **2008**, *47*, 6647. (e) Zhu, Y. G.; Zhai, C. W.; Yang, L. P.; Hu, W. H. *Chem. Commun.* **2010**, *46*, 2865.

[3] For selected MCRs via the trapping of ammonium ylides, see: (a) Jiang, J.; Xu, H.-D.; Xi, J.-B.; Ren, B.-Y.; Lv, F.-P.; Guo, X.; Jiang, L.-Q.; Zhang, Z.-Y.; Hu, W.-H. *J. Am. Chem. Soc.* **2011**, *133*, 8428. (b) Zhu, Y.; Zhai, C.; Yang, L.; Hu, W. *Eur. J. Org. Chem.* **2011**, *2011*, 1113. (c) Zhou, C.-Y.; Wang, J.-C.; Wei, J.; Xu, Z.-J.; Guo, Z.; Low, K.-H.; Che, C.-M. *Angew. Chem., Int. Ed.* **2012**, *51*, 11376. (d) Song, J.; Guo, C.; Adele, A.; Yin, H.; Gong, L.-Z. *Chem.—Eur. J.* **2013**, *19*, 3319. (e) Jiang, J.; Ma, X.; Liu, S.; Qian, Y.; Lv, F.; Qiu, L.; Wu, X.; Hu, W. *Chem. Commun.* **2013**, *49*, 4238.

[4] For MCRs via the trapping of zwitterionic intermediate, see: (a) Qiu, H.; Li, M.; Jiang, L.-Q.; Lv, F.-P.; Zan, L.; Zhai, C.-W.; Doyle, M. P.; Hu, W.-H. *Nat. Chem.* **2012**, *4*, 733. (b) Li, M.; Zan, L.; Prajapati, D.; Hu, W. *Org. Biomol. Chem.* **2012**, *10*, 8808. (c) Xing, D.; Jing, C.; Li, X.; Qiu, H.; Hu, W. *Org. Lett.* **2013**, *15*, 3578.

[5] Amine poisoning effect with rhodium catalysts has been reported; see: (a) Aller, E.; Buck, R. T.; Drysdale, M. J.; Ferris, L.; Haigh, D.; Moody, C. J.; Pearson, N. D.; Sanghera, J. B. *J. Chem. Soc., Perkin Trans. 1* **1996**, *0*, 2879. (b) Aviv, I.; Gross, Z. *Chem.—Eur. J.* **2008**, *14*, 3995.

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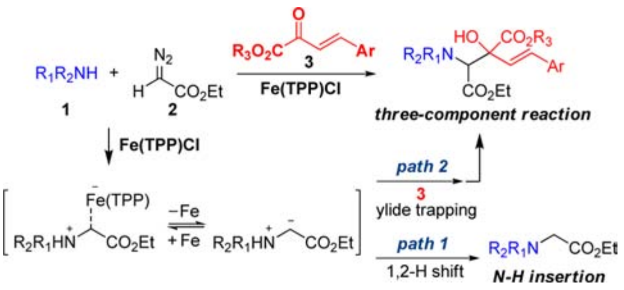
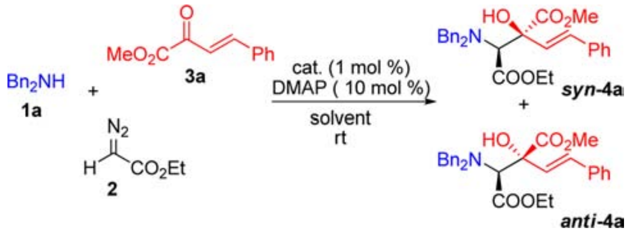
amines could be used, and to avoid undesired side reactions such as dimerization, gradual addition of the diazo compounds is generally required, thus limiting the synthetic value of such methodologies.[3] On the other hand, rhodium catalysts are relatively expensive. Toward these ends, the search for alternatively efficient yet cheap and widely available metal catalysts that can overcome the above-mentioned drawbacks of rhodium catalysts is of great importance for both the development of new types of MCRs and economic considerations.[1f,g]

Scheme 1. Iron Porphyrin-Catalyzed Three-Component Reaction



Metalloporphyrins have been found to be efficient catalysts to decompose diazo compounds for a range of useful transformations;[6] among them, iron porphyrins have shown great efficiency in catalyzing N−H insertion of amines.[5b,7,8] Due to the unique ligand environment and metal coordination modes, both aliphatic and aromatic amines could undergo efficient N−H insertions with iron porphyrin catalysts. In view of its unique catalytic feature, we intend to develop new MCRs starting from aliphatic amines by applying iron porphyrin catalyst. Related mechanistic studies have revealed that the generation of a ylide intermediate and further proton transfer are involved in iron porphyrin-catalyzed N−H insertions (Scheme 1, path 1).[5b] We envisioned that suitable electrophiles may be able to trap this Fe-associated ylide intermediate for a three-component reaction (Scheme 1, path 2). If this strategy works, it will not only provide further evidence for the existence of ylide intermediate in iron porphyrin-catalyzed N−H insertion process, but will also provide a unique method for the synthesis of β-hydroxy-α-amino ester derivatives starting from ethyl diazoacetate and aliphatic amines.

Table 1. Reaction Condition Optimization[a]



entry	cat.	solvent	yield[b] (%)	dr (*syn*:*anti*)[c]
1	Fe(TPP)Cl	CH_2Cl_2	73	69:31
2	$Rh_2(OAc)_4$	CH_2Cl_2	<5	
3[d]	$CuPF_6(MeCN)_4$	CH_2Cl_2	<5	
4[d]	$Cu(OTf)_2$	CH_2Cl_2	<5	
5[d]	Fe(TPP)Cl	CH_2Cl_2	73	69:31
6	Fe(TPP)Cl	toluene	65	71:29
7	Fe(TPP)Cl	DCE	68	74:26
8	Fe(TPP)Cl	$CHCl_3$	77	75:25
9	Fe(TPP)Cl	EtOAc	64	73:27
10	Fe(TPP)Cl	Et_2O	75	71:29
11[e]	Fe(TPP)Cl	$CHCl_3$	27	75:25
12		$CHCl_3$	<5	

[a] Reaction conditions: to a solution of **1a** (0.15 mmol), **3a** (0.1 mmol), Fe(TPP)Cl (1 mol %), and DMAP (10 mol %) in 1 mL of solvent was added **2** (0.15 mmol) in 1 mL of solvent in one portion. [b] Isolated yield. [c] Determined by crude ^{1}HNMR. [d] 5 mol % of catalyst was used. [e] Reaction was carried out at 10 °C.

As the starting point, dibenzylamine (**1a**) was chosen as the amine source to react with EDA (**2**) and β,γ-unsaturated α-keto ester (**3**). The reason to choose a secondary amine as the substrate is to avoid undesired double N−H insertions;[9] on the other hand, the dibenzyl group can be easily removed under hydrogenation for further functionalization. The initial exploration was conducted with the use of 1 mol % of Fe(TPP)Cl (TPP: *meso*-tetraphenylporphyrin) and 10 mol % of DMAP with CH_2Cl_2 as the solvent.[10] To our great delight, the desired three-component product **4a** via an exclusively aldol-type addition was produced in 73% yield with a 69:31 diastereoselectivity (Table 1, entry 1). The excellent regioselectivity of this reaction for 1,2-addition rather than 1,4-addition may come from the hard basicity character of the ammonium ylide generated from EDA and iron carbene complex.[2e] On the other hand, when $Rh_2(OAc)_4$ was chosen as the catalyst, neither N−H insertion product nor three-component product was detected due to serious catalyst poisoning (Table 1, entry 2). $CuPF_6(MeCN)_4$ and $Cu(OTf)_2$, which had been previously used as efficient

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(6) For leading reviews on metalloporphyrin-catalyzed transformations, see: (a) Ruppel, J. V.; Fields, K. B.; Snyder, N. L.; Zhang, X. P. In *Handbook of Porphyrin Science*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; World Scientific: London, 2010; Vol. 10, Chapter 43, pp 1−84. (b) Lu, H.; Zhang, X. P. *Chem. Soc. Rev.* **2011**, *40*, 1899.

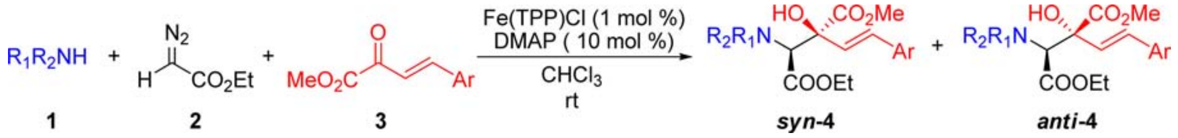
(7) (a) Aviv, I.; Gross, Z. *Synlett* **2006**, 951. (b) Baumann, L. K.; Mbuvi, H. M.; Du, G.; Woo, L. K. *Organometallics* **2007**, *26*, 3995. (c) Mbuvi, H. M.; Klobukowski, E. R.; Roberts, G. M.; Woo, L. K. *J. Porphyrins Phthalocyanines* **2010**, *14*, 284. (d) Anding, B. J.; Woo, L. K. *Organometallics* **2013**, *32*, 2599.

(8) For selected examples of iron-catalyzed asymmetric X−H insertions, see: (a) Zhu, S. F.; Cai, Y.; Mao, H. X.; Xie, J. H.; Zhou, Q. L. *Nat. Chem.* **2010**, *2*, 546. (b) Cai, Y.; Zhu, S. F.; Wang, G. P.; Zhou, Q. L. *Adv. Synth. Catal.* **2011**, *353*, 2939.

(9) Double N−-H insertions have been observed in the iron porphyrin-catalyzed reaction between EDA and aniline; see ref 7b.

(10) DMAP was generally used as an additive in metalloporphyrin-catalyzed transformations for its coordinating effects; for selected examples, see: (a) Chen, Y.; Fields, K. B.; Zhang, X. P. *J. Am. Chem. Soc.* **2004**, *126*, 14718. (b) Lai, T.-S.; Chan, F.-Y.; So, P.-K.; Ma, D.-L.; Wong, K.-Y.; Che, C.-M. *Dalton Trans.* **2006**, *0*, 4845. (c) Chen, Y.; Ruppel, J. V.; Zhang, X. P. *J. Am. Chem. Soc.* **2007**, *129*, 12074. (d) Morandi, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 938.

Table 2. Substrate Scope of the Iron Porphyrin-Catalyzed Three-Component Reaction[a]



entry	1	Ar	4	yield[b] (%)	dr (*syn*:*anti*)[c]
1	Bn_2NH (**1a**)	Ph	**4a**	77	75:25
2	Bn_2NH (**1a**)	*p*-MePh	**4b**	78	75:25
3	Bn_2NH (**1a**)	*p*-BrPh	**4c**	64	74:26
4	Bn_2NH (**1a**)	*p*-ClPh	**4d**	66	75:25
5	Bn_2NH (**1a**)	*p*-FPh	**4e**	64	74:26
6	Bn_2NH (**1a**)	*m*-MePh	**4f**	70	77:23
7	Bn_2NH (**1a**)	*m*-BrPh	**4g**	63	72:28
8	Bn_2NH (**1a**)	*m*-NO_2Ph	**4h**	75	77:23
9	Bn_2NH (**1a**)	2-thienyl	**4i**	72	75:25
10	MeBnNH (**1b**)	Ph	**4j**	73	73:27
11	Et_2NH (**1c**)	Ph	**4k**	65	69:31
12	pyrrolidine (**1d**)	Ph	**4l**	62	62:38
13	*t*-$BuNH_2$ (**1e**)	Ph	**4m**	83	59:41
14	$(CO_2Et)_2CHNH_2$ (**1f**)	Ph	**4n**	88	50:50
15	$PhNH_2$ (**1g**)	Ph	**4o**	82	80:20

[a] Reaction conditions: to a solution of **1** (0.45 mmol), **3** (0.3 mmol), Fe(TPP)Cl (1 mol %), and DMAP (10 mol %) in 1 mL of $CHCl_3$ was added dropwise **2** (0.45 mmol) in 1 mL of $CHCl_3$. [b] Isolated yield. [c] Determined by crude ^1H NMR.

catalysts for MCRs of EDA with anilines and β,γ-unsaturated α-keto esters,[2e] were also proven to be ineffective (Table 1, entries 3 and 4). With Fe(TPP)Cl as the catalyst, further condition optimization was conducted by the screening of solvents, the reaction run smoothly in different solvents with similar yields and diastereoselectivities while highest yield (77%) as well as diastereoselectivity (75:25) were achieved when $CHCl_3$ was used (Table 1, entries 5−10), these results indicated that this reaction had a very subtle solvent effect. Lowering the reaction temperature to 10 °C resulted in no improvement of the diastereoselectivity but a greatly decreased yield (Table 1, entry 11). Control experiments revealed that Fe(TPP)Cl is indispensable for this reaction (Table 1, entry 12). In the absence of DMAP, the reaction could proceed but suffered a longer reaction time and poor reproducibility.[10] It is worth mentioning that this reaction could be run in a practical one-pot fashion and gradual addition of EDA was not necessary, therefore making it more practical and convenient to operate.

With the optimized reaction conditions in hand, a wide range of substituted β,γ-unsaturated α-keto esters were evaluated. Substrates bearing different *para*- or *meta*-substituted aryl rings were first tested, and the desired β-hydroxy-α-amino ester products were obtained in good yields with about 3:1 diastereoselectivities regardless of the substitution patterns (Table 2, entries 1−8). Substrates bearing a 2-thienyl group also provided the corresponding product in good yield with similar diastereoselectivity (Table 2, entry 9). Different types of secondary amines were also tested. When benzylmethylamine (**1b**) was chosen as the substrate, the three-component reaction proceeded smoothly to provide the desired product in good yield and diastereoselectivity (Table 2, entry 10); however, the use of either diethylamine (**1c**) or pyrrolidine (**1d**) as the substrate resulted in slightly lower diastereoselectivities (Table 2, entries 11 and 12). Primary aliphatic amines generally underwent double N−H insertions rather than the desired three-component reaction;[11] however, when bulky aliphatic amines such as *tert*-butyl amine (**1e**) or diethyl aminomalonate (**1f**) were used, the desired products were obtained in high yields, albeit with decreased diastereoselectivities (Table 2, entries 13 and 14). The reaction of diethyl aminomalonate offered an efficient way for the synthesis of an intriguing type of peptide chains. Aniline (**1g**) was also good substrate for this iron prophyrin-catalyzed three-component transformation, affording the desired product in good yield with slightly higher diastereoselectivity (Table 2, entry 15). The relative stereochemistry of products was assigned as *syn* in analogy with *syn*-**4c** as determined by single-crystal X-ray diffraction (Figure 1).[12]

The dibenzyl group of the product could be readily removed by hydrogenation.[13] Under standard reaction conditions, the alkene moiety in the product was also

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(11) For example, when benzylamine was chosen as the substrate, the double N−H inserted product was afforded as the major product.

(12) CCDC 934240 (*syn*-**4c**) contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(13) Caddick, S.; Parr, N. J.; Pritchard, M. C. *Tetrahedron* **2001**, *57*, 6615.

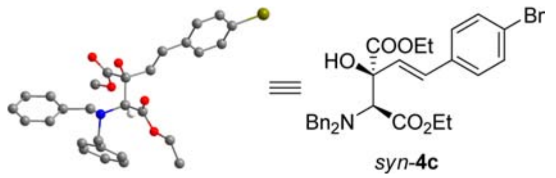
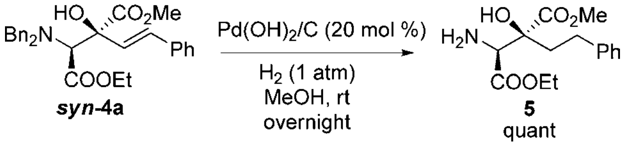


Figure 1. X-ray structure of *syn*-**4c**.

Scheme 2. Deprotection of *syn*-**4a** by Hydrogenation



hydrogenated (Scheme 2). Therefore, the β-hydroxy-α-amino ester product possessing a primary amine unit could be easily further functionalized for the synthesis of densely substituted biologically intriguing amino acid derivatives.

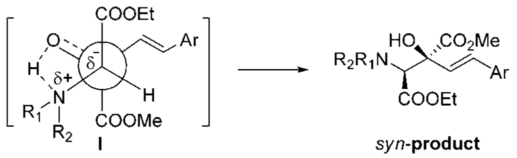


Figure 2. Proposed transition state for the formation of *syn*-products.

A plausible mechanism for this iron-catalyzed three-component reaction was proposed. This three-component transformation should start with the generation of an iron carbene intermediate from EDA and Fe(TPP)Cl.[14] The carbene carbon then undergoes nucleophilic attack by amine to form an ammonium ylide intermediate,[15] which, in the presence of β,γ-unsaturated α-keto ester as a relatively active electrophile, undergoes an aldol-type addition to give the three-component product. We proposed an intermolecular hydrogen bonding between the ylide intermediate and the carbonyl group of β,γ-unsaturated α-keto ester would facilitate the subsequent aldol-type trapping process, and *syn*-product could be obtained via the proposed transition state I (Figure 2). The exact role of the additive DMAP is unclear, but it may act as an unhindered base to coordinate with Fe(TPP)Cl and thus facilitate the metal carbene formation step.[5b,7b,10]

In summary, an iron porphyrin-catalyzed three-component reaction of diazo compounds with aliphatic amines and β,γ-unsaturated α-keto esters has been developed for the synthesis of β-hydroxy-α-amino esters. With the unique ligand environment and mild catalytic feature of iron porphyrin, we were able to develop a MCR starting from aliphatic amines for the first time by overcoming the catalyst poisoning issue existed in rhodium-catalyzed transformations, and allow this reaction to be conducted in a practical one-pot fashion. This iron porphyrin-catalyzed system offers a unique platform for the development of new asymmetric MCRs by either the use of chiral porphyrins or cooperative catalysis between iron porphyrin and basic chiral organocatalysts. Related studies are currently underway in our laboratory.

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Supporting Information Available. Typical experimental procedure and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(14) The formation of iron carbene complexes between iron porphyrins and diazo compounds has been previously confirmed by X-ray crystal analysis; see: (a) Mansuy, D.; Lange, M.; Chottard, J. C.; Bartoli, J. F.; Chevrier, B.; Weiss, R. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 781. (b) Li, Y.; Huang, J. S.; Zhou, Z. Y.; Che, C. M.; You, X. Z. *J. Am. Chem. Soc.* **2002**, *124*, 13185.

(15) Alternatively, Gross and co-workers proposed a mechanism involving a direct nucleophilic attack from aromatic amine to EDA in the assistant of iron coordination rather than a metal carbene intermediate to generate an ammonium ylide; see ref 5b.